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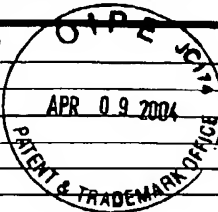
Date Submitted: April 9, 2004

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Sheet 1 of 1

**Complete if Known**

Application Number 10/618,835  
 Filing Date 07/15/2003  
 First Named Inventor John P. Cooke  
 Group Art Unit 1654  
 Examiner Name J. Russel  
 Attorney Docket Number 080618-0237



**U.S. PATENT DOCUMENTS**

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|                    |                       | Number               | Kind Code <sup>2</sup> (if known) |   |  |   |
| JR                 | D1                    | 5,372,807            |                                   | POIANI et al.                                   | 12-13-1994                                       | 424/78,36   |
| JR                 | D2                    | 5,278,189            |                                   | RATH et al.                                     | 01-11-1994                                       | 514/561   |
|                    |                       |                      |                                   |   |  |   |
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| JR                 | D3                    |                         | WO 88/01872         |                                   | Dudrick Medical Research                         | 03-24-1988                                       |   |                |
| JR                 | D4                    |                         | EP 0 483 614 A      |                                   | NB Int'l. Technologies                           | 05-06-1992                                       |   |                |
| JR                 | D5                    |                         | WO 94/16729 A       |                                   | Neorx Corporation                                | 08-04-1994                                       |   |                |
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| JR                 | D7                    |                         | EP 0 546 796 A1     |                                   | Ajinomoto Co., Inc.                              | 06-16-1993                                       |   |                |
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| JR                 | D9                    |                         | GB 1,304,499        |                                   | Tixier, Madeleine                                | 01-24-1973                                       |   |                |
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**NON PATENT LITERATURE DOCUMENTS**

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|--------------------|-----------------------|--|----------------|
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| JR                 | D11                   | IGNARRO, LOUIS J., et al., "Basic Polyamino Acids Rich in Arginine, Lysine, or Ornithine Cause Both Enhancement of and Refractoriness to Formation of Endothelium-Derived Nitric Oxide in Pulmonary Artery and Vein," <i>Circulation Research</i> , vol. 64, no. 2, 1989, pages 315-329. |                |
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| Examiner Signature | Jeffrey E. Russel | Date Considered | September 8, 2004 |
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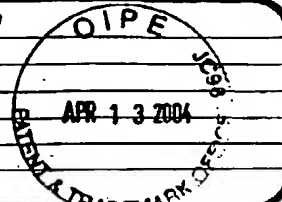
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|                       |                          |  |                |

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Jeffrey E. Russel

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September 8, 2004

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| JR                 | A7                    | 4,900,566            |                                   | HOWARD  | 02-13-1990                                       | 426/72  |
| JR                 | A8                    | 4,920,098            |                                   | COTTER et al.                                   | 04-24-1990                                       | 514/2   |
| JR                 | A9                    | 4,957,938            |                                   | ANDERSON et al.                                 | 09-18-1990                                       | 514/412   |
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| JR                 | A19                   | 5,221,668            |                                   | HENNINGFIELD et al.                             | 06-22-1993                                       | 514/23  |
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| JR                 | A21                   | 5,262,435            |                                   | JOSHUA et al.                                   | 11-16-1993                                       | 514/452   |
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| JR                 | A25                   | 5,326,569            |                                   | ACOSTA et al.                                   | 07-05-1994                                       | 424/440   |
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| JR                 | A27                   | 5,364,644            |                                   | WALASZEK et al.                                 | 11-15-1994                                       | 514/574   |
| JR                 | A28                   | 5,374,651            |                                   | KILBOURN et al.                                 | 12-20-1994                                       | 514/400   |
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| JR                 | A31                   | 5,428,070            |                                   | COOKE et al.                                    | 06-27-1995                                       | 514 / 557   |
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| JR                 | A35                   | 5,576,351            |                                   | YOSHIMURA et al.                                | 11-19-1996                                       | 514/565   |
| JR                 | A36                   | 5,626,883            |                                   | PAUL  | 05-06-1997                                       | 424/605   |
| JR                 | A37                   | 5,631,031            |                                   | MEADE   | 05-20-1997                                       | 426/2   |
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| JR                 | A40                   | 5,780,039            |                                   | GREENBERG                                       | 07-14-1998                                       | 424/400   |
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| JR                 | A42                   | 5,891,459            |                                   | COOKE et al.                                    | 04-06-1999                                       | 424 / 439   |
| JR                 | A43                   | 5,965,529            |                                   | GARFIELD et al.                                 | 10-12-1999                                       | 514/12  |

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Signature

Jeffrey E. Russel

Date  
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September 7, 2004

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 426 / 541  
 514 / 263, 32  
 514 / 423

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| JR                 | A48                   | JP                      | 50-48189            |                                   |  | 04-30-1975                                       |  |                |
| JR                 | A49                   | JP                      | 57-5692             |                                   |  | 01-12-1982                                       |  |                |
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| JR                 | A52                   | EP                      | 0441119A2           |                                   | LEVERE et al.                                    | 08-14-1991                                       |  |                |
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| JR                 | A54                   | EP                      | 0511587             |                                   | MORIYAMA   | 11-04-1992                                       |  |                |
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| JR                 | A56                   | EP                      | 0546796A1           |                                   | SONAKA   | 06-16-1992                                       |  |                |
| JR                 | A57                   | ZA                      | 93-6619             |                                   | DAVIS et al.                                     | 09-15-1993                                       |  |                |
| JR                 | A58                   | WO                      | 93-18156            |                                   | BLOCH et al.                                     | 09-16-1993                                       |  |                |
| JR                 | A59                   | JP                      | 7-163269            |                                   |  | 06-27-1995                                       |  |                |
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| JR                 | A62                   | DI ROSA; "Azione antiammoniacale ed epatoprotettiva di una associazione a base di pirrolidonecarbossilato di arginina, taurina e vitamina B <sub>6</sub> "; <i>Lavoro ricevuto</i> (July 14, 1967).  |                |
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| JR                 | A64                   | KADIRVEL et al.; "Uptake of L-Arginine and L-Lysine by the small intestine and its influence on Arginine-Lysine antagonism in chicks"; <i>Journal of Nutrition</i> , Vol. 103, No. 3 (March, 1974), pp. 339-43.  |                |

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| Filing Date            | 07/15/2003    |
| First Named Inventor   | John P. Cooke |
| Group Art Unit         | 1654          |
| Examiner Name          | J. Russel     |
| Attorney Docket Number | 080618-0237   |

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| Filing Date            | 07/15/2003    |
| First Named Inventor   | John P. Cooke |
| Group Art Unit         | 1654          |
| Examiner Name          | J. Russel     |
| Attorney Docket Number | 080618-0237   |

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|  |   | Group Art Unit           | 1654          |
|  |   | Examiner Name            | J. Russel     |
| Date Submitted: April 19, 2004                           |   | Attorney Docket Number   | 080618-0237   |
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Date  
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Date Submitted: April 19, 2004

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|------------------------|---------------|
| Application Number     | 10/618,835    |
| Filing Date            | 07/15/2003    |
| First Named Inventor   | John P. Cooke |
| Group Art Unit         | 1654          |
| Examiner Name          | J. Russel     |
| Attorney Docket Number | 080618-0237   |

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|  |    | First Named Inventor     | John P. Cooke |
|  |    | Group Art Unit           | 1654          |
|  |    | Examiner Name            | J. Russel     |
| Date Submitted: April 19, 2004                           |    | Attorney Docket Number   | 080618-0237   |
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| JR                                      | A228                  | D. PEARSON and S. SHAW, <u>The Life Extension Companion</u> , Warner Books (1984), NY, pp. cover to cover (1325 pages total).   |                |
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| JR                                      | A230                  | Derwent Abstract of JP 50048189 A, 04/30/1975, "Fermentative production of L-arginine - in presence of antibiotics, surfactants and antioxidants," 1 page.  |                |
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| JR                                      | A234                  | Derwent Abstract of EP 441119 A, 08/14/1991, "Use of L-arginine - to treat high vascular resistance disorders, e.g. hypertension and bronchial asthma," 2 pages.  |                |
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| JR                                      | A236                  | Derwent Abstract of EP 511118 A, 10/28/1992, "Use of lysine and arginine pyrrolidone carboxylate(s) as anti-oxidants - preferably with a phenolic derivative, e.g. tocopherol, in pharmaceutical and cosmetic compositions, particularly to protect skin from ageing," 2 pages. |                |
| JR                                      | A237                  | Derwent Abstract of EP 546796 A, 06/16/1993, "Use of L-arginine - for treating and preventing atherosclerosis," 1 page.   |                |
| JR                                      | A238                  | Inpadoc Abstract of ZA 9410015 A, 11/08/1995, "A pharmaceutical composition," 1 page.   |                |
| JR                                      | A239                  | Derwent Abstract of WO 9318156 A, 09/16/1993, "Endothelial nitric oxide synthase and gene - which catalyses nitric oxide formation, for, e.g., inhibiting platelet aggregation or smooth muscle cell proliferation," 1 page.  |                |
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|--------------------|-------------------|-----------------|-------------------|
| Examiner Signature | Jeffrey E. Russel | Date Considered | September 7, 2004 |
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STATEMENT BY APPLICANT**

Date Submitted: May 19, 2004

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**Complete if Known**

Application Number 10/618,835  
 Filing Date 7/15/2003  
 First Named Inventor John P. Cooke  
 Group Art Unit 1654  
 Examiner Name J. Russel  
 Attorney Docket Number 080618-0237

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|                    |                       | Number               | Kind Code <sup>2</sup> (if known) |   |  |   |
| JR                 | F1                    | 4,900,566            |                                   | Howard  | 2/13/1990  | 426/72  |
| JR                 | F2                    | 5,106,836            |                                   | Clemens et al.                                  | 4/21/1992  | 514/21  |

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| JR                 | F3                    | EP                      | 0511587             | A1                                | Takeda Chemical Industries, Ltd.                 | 11/04/1992                                       |   |                |

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|--------------------|-----------------------|--|----------------|
| JR                 | F4                    | JP60094075A, AJINOMOTO KK; Dialog Japanese Abstract (1 pg.) (May 27, 1985)   |                |
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| JR                 | F8                    | JP60049764A, AJINOMOTO KK, Dialog Japanese Abstract (1 pg.) (March 19, 1985)   |                |
| JR                 | F9                    | European Search Report dated 7/31/03 for EP Application No. 107776.2   |                |

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Jeffrey E. Russel

Date Considered

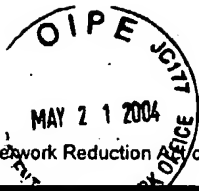
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### INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: May 21, 2004

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| <i>JR</i>          | C1                    | 2002/0091160         | A1                                | COOKE, et al.                                   | 02-01-2002                                       | <i>574/564</i>  |
| <i>JR</i>          | C2                    | 5,026,721            |                                   | DUDRICK, et al.                                 | 06-25-1991                                       |   |
| <i>JR</i>          | C3                    | 5,028,627            |                                   | KILBOURN, et al.                                | 07-02-1991                                       |   |
| <i>JR</i>          | C4                    | 6,117,872            |                                   | MAXWELL, et al.                                 | 09-12-2000                                       |   |
| <i>JR</i>          | C5                    | 6,337,321            |                                   | COOKE, et al.                                   | 01-08-2002                                       |   |
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| <i>JR</i>          | C8                    | EP                      | 0 259 167 A2        |                                   | Millman  | 03-09-1988                                       |   |                |
| <i>JR</i>          | C9                    | EP                      | 0 511 118 A1        |                                   | N'Guyen  | 10-28-1992                                       |   |                |
| <i>JR</i>          | C10                   | EP                      | 511 587 A1          |                                   | Moriyama et al.                                  | 11-04-1992                                       |   |                |
| <i>JR</i>          | C11                   | EP                      | 0 546 796 A1        |                                   | Sonaka et al.                                    | 06-16-1993                                       |   |                |
| <i>JR</i>          | C12                   | WO                      | 98/18491            |                                   | Burgstiner                                       | 05-07-1998                                       |   |                |
| <i>JR</i>          | C13                   | ZA                      | 9410015 A           |                                   | Davis et al.                                     | 11-08-1995                                       |   |                |
| <i>JR</i>          | C14                   | FR                      | 2 507 892           |                                   | Brugioni et al.                                  | 12-24-1982                                       |   |                |
| <i>JR</i>          | C14a                  | GB                      | 2 100 982           |                                   | Brugioni et al.                                  | 06-22-1982                                       |   |                |
| <i>JR</i>          | C15                   | WO                      | 85/00517            |                                   | Niebes et al.                                    | 02-14-1985                                       |   |                |

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| <i>JR</i>          | C16                   | Adams et al., "Oral L-arginine improves endothelium-dependent dilatation and reduces monocyte adhesion to endothelial cells in young men with coronary artery disease" <i>Atherosclerosis</i> , 1997, 129(2):261-69.   |                |
| <i>JR</i>          | C17                   | Adams et al., "Cigarette smoking is associated with increased human monocyte adhesion to endothelial cells: reversibility with oral L-arginine but not vitamin C," <i>J. Amer. Coll. Cardiol.</i> , 1997, 29(3):491-97.  |                |

Examiner Signature

*Jeffrey E. Russel*

Date Considered

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| JN                 | C19                   | Aisaka et al., "N <sup>G</sup> -monomethyl-L-arginine, an inhibitor of endothelium-derived nitric oxide synthesis, abbreviates acetylcholine-induced vasodilatation in the guinea-pig" in <i>Nitric Oxide from L-arginine: a Bioregulatory System</i> (S. Moncada and E.A. Higgs, eds.), 1990, Chapter 40, pp. 379-384. |                |
| JN                 | C20                   | Aisaka et al., "Modulation of cardiovascular function by L-arginine-derived nitric oxide" <i>Frontiers and new horizons in amino acid research</i> (K. Takai, ed.), 1992, 437-442.  |                |
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| JN                 | C22                   | Alba-Roth et al., "Arginine stimulates growth hormone secretion by suppressing endogenous somatostatin secretion," <i>J. Clin. Endocrinol. Metab.</i> , 1988, 67(6):1186-89.  |                |
| JN                 | C23                   | Amrani et al., "Role of basal release of nitric oxide on coronary flow and mechanical performance of the isolated rat heart," <i>J. Physiol.</i> , 1992, 456:681-87.  |                |
| JN                 | C24                   | Aoyama et al., "Effects on liver and serum lipids of dietary supplements of methionine and excess lysine given to previously-starved rats," <i>British J. Nutr.</i> , 1983, 50(3):627-36.   |                |
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| JN                 | C28                   | Barbul et al., "Arginine: a thymotropic and wound-healing promoting agent," 1977, <i>Surg. Forum.</i> 28:101-103.   |                |
| JN                 | C29                   | Barclay et al., "The role of blood flow in limiting maximal metabolic rate in muscle," 1975, <i>Med Sci Sports.</i> 7(2):116-119.   |                |
| JN                 | C30                   | Baumier et al., "Arginine: new and exciting developments for an 'old' amino acid," 1996, <i>Biomed. Environ. Sci.</i> 9(2-3):296-315.   |                |
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| First Named Inventor   | John P. Cooke |
| Group Art Unit         | 1654          |
| Examiner Name          | J. Russel     |
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| JR                 | C32                   | Bissell, "Porphyria," Textbook of Medicine (ed. Wyngaarden and Smith), W.B. Saunders Co., Harcourt Brace Jovanovich Inc. Philadelphia, 1988, pp. 1182-89.  |                |
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| First Named Inventor   | John P. Cooke |
| Group Art Unit         | 1654          |
| Examiner Name          | J. Russel     |
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|  |   | First Named Inventor     | John P. Cooke |
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|  |   | Examiner Name            | J. Russel     |
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| <i>JR</i>                       | C58                   | Church et al., "Hypertension and renal impairment as complications of acute porphyria" Nephrol Dial Transplant. 1992, 7(10):986-90.  |                |
| <i>JR</i>                       | C59                   | Cooke et al., "Endothelial dysfunction in hypercholesterolemia is corrected by L-arginine" Basic Res Cardiol., 1991, 86 Suppl 2:173-81.  |                |
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| <i>JR</i>                       | C61                   | Creager et al., "L-arginine improves endothelium-dependent vasodilation in hypercholesterolemic humans" Supplement to Circulation 1990, 82:III-346, 1248-1253.   |                |
| <i>JR</i>                       | C62                   | Cynober et al., "Arginine metabolism in mammals" J. Nutr. Biochem. 1995, 6:402-13.   |                |
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| <i>JR</i>                       | C64                   | de Graaf JC et al., "Nitric oxide functions as an inhibitor of platelet adhesion under flow conditions". Circulation 1992, (6):2284-90.  |                |
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| <i>JR</i>                       | C66                   | Dhanakoti et al., "Net renal arginine flux in rats is not affected by dietary arginine or dietary protein intake" Nutrient Metabolism 1992, 122(5):1127-34.  |                |
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| <i>JR</i>                       | C71                   | Elder et al., "Treatment of acute porphyria" Hosp Med. 2001, 62(7):422-25.   |                |

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|   |   | Examiner Name            | J. Russel     |
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| Jn                              | C72                   | Feng Q., et al., "Endothelium-derived relaxing factor (EDRF) and nitric oxide (NO). I. Physiology, pharmacology and pathophysiological implications" Clin. Physiol. 1990, (5):407-26.  |                |
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| JR                              | C86                   | Furchgott, RF, "The role of endothelium in the responses of vascular smooth muscle to drugs" Ann. Rev. Pharmacol. Toxicol. 1984, 24:175-97.  |                |
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| Application Number     | 10/618,835    |
| Filing Date            | 07/15/2003    |
| First Named Inventor   | John P. Cooke |
| Group Art Unit         | 1654          |
| Examiner Name          | J. Russel     |
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|--------------------|-----------------------|--|----------------|
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Jeffrey E. Russel

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|   |   | First Named Inventor     | John P. Cooke |
|   |   | Group Art Unit           | 1654          |
|   |   | Examiner Name            | J. Russel     |
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|   |    | First Named Inventor     | John P. Cooke |
|   |    | Group Art Unit           | 1654          |
|   |    | Examiner Name            | J. Russel     |
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| Examiner Signature | Jeffrey E. Russel | Date Considered | September 7, 2004 |
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| Application Number     | 10/618,835    |
| Filing Date            | 07/15/2003    |
| First Named Inventor   | John P. Cooke |
| Group Art Unit         | 1654          |
| Examiner Name          | J. Russel     |
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|   |    | Filing Date              | 07/15/2003    |
|   |    | First Named Inventor     | John P. Cooke |
|   |    | Group Art Unit           | 1654          |
|   |    | Examiner Name            | J. Russel     |
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| Examiner Signature | Jeffrey E. Russel | Date Considered | September 7, 2004 |
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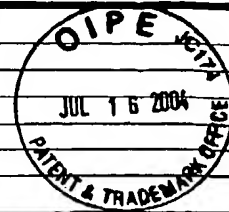
**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

**Date Submitted: July 16, 2004**

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| <b>Application Number</b>     | 10/618,835    |
| <b>Filing Date</b>            | 7/15/2003     |
| <b>First Named Inventor</b>   | John P. Cooke |
| <b>Group Art Unit</b>         | 1654          |
| <b>Examiner Name</b>          | J. Russel     |
| <b>Attorney Docket Number</b> | 080618-0237   |



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| JR                 | G23                   | LEFER ET AL., "Role of Endothelium-derived Relaxing Factor as a Cardioprotective Agent in Myocardial Ischemia", <i>Basil, Karger</i> (1990), pp. 190-197.  |                |
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| JR                 | G34                   | BAI, et al. <i>Ann. Thorac. Surg.</i> , Vol. 66, pp. 814-820 (1998).   |                |
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| JR                 | G37                   | ORKIN, et al. "Report and Recommendations of the Panel to Assess the NIH Investment on Research in Gene Therapy", (1995).  |                |
| JR                 | G38                   | ROČIĆ ET AL., "L-arginyl-L-lysine and L-arginyl-L-arginine", <i>Med. Sci. Res.</i> (1990), Vol. 18, pp. 165-166.   |                |
| JR                 | G39                   | ADAMS ET AL., "Oral L-Arginine Inhibits Platelet Aggregation but Does Not Enhance Endothelium-Dependent Dilation in Healthy Young Men", <i>JACC</i> (October 1995), Vol. 26, No. 4, pp. 1054-1061.   |                |
| JR                 | G40                   | MAYER ET AL., "Homocysteine and Coronary Atherosclerosis," <i>JACC</i> (March 1, 1996), Vol. 27, No. 3, pp. 517-527.   |                |
| JR                 | G41                   | Supplementary European Search Report dated May 12, 2004 for EP Application No. 97938163.9  |                |
| JR                 | G42                   | International Search Report dated August 29, 1994 for PCT Application No. PCT/US94/06203.  |                |
| JR                 | G43                   | International Search Report dated January 21, 1997 for PCT Application No. PCT/US96/17241.   |                |
| JR                 | G44                   | International Search Report dated October 10, 1997 for PCT Application No. PCT/US97/13905.   |                |

 Examiner  
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 Date  
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